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14. ABSTRACT

Activities during this second year of the project were focused on Tasks 1 and 2 of the statement of work, as planned. Task 1 (months 1-30) is to obtain blood and data for 300 new study subjects. In the past year, 59 men were enrolled in the study (Task 1.a), for a total of 612 men towards our goal of 800 men. Among enrolled men, blood was collected on 41 men (Task 1.b), for a total of 483 blood samples. 29 pre-treatment blood samples were collected (Task 1.c), for a total of 115 towards our goal of 150 pre-treatment samples. Questionnaires were completed by 60 men (Task 1.d), for a total of 589 completed questionnaires. Our enrollment rate among eligible men continues to be ~95%. Related to Task 2, we have actively followed all of the enrolled men in the cohort (from the previously funded study and from the current protocol) who did not have extensive disease at diagnosis for PSA outcomes. Mean follow-up time is currently 57 months. Follow-up of PSA test results through medical records and Caisis database have just been updated, and a linkage with Metropolitan Detroit SEER registry (MDCSS) will be repeated prior to final analyses.

15. SUBJECT TERMS
prostate cancer, microRNA, racial disparities, African American, genetic polymorphisms, biochemical recurrence, epidemiology

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1. Introduction

In the US, African American (AA) men are at 60% higher risk of developing prostate cancer (PCa) than European American (EA) men, and AA men are 2.4 times more likely to die from PCa than EA men.[1] The objective of this study is to identify novel genetic and epigenetic factors that might contribute significantly to racial/ethnic disparity in PCa risk and progression. We will examine the association of inherited polymorphisms in genes in the microRNA (miRNA) biogenesis pathway as well as the association of plasma miRNA levels with prostate cancer aggressiveness and biochemical recurrence (BCR) among 480 AA and 320 EA men with PCa from the Karmanos Cancer Institute (KCI) in Detroit, MI. Little is known about the role of microRNAs (miRNAs) and their biogenesis in prostate cancer (PCa), and less is understood about the possible race-specific role of miRNAs in PCa aggressiveness and outcomes. We hypothesize that polymorphisms in genes in the miRNA biogenesis pathway and plasma miRNA levels are potential prognostic indicators for PCa aggressiveness and/or outcome and that these associations may be linked to race. The specific aims of this project are to 1) determine the associations between polymorphisms in genes within the miRNA biogenesis pathway and (a) PCa aggressiveness and (b) biochemical recurrence in AA and EA men with PCa, 2) determine the associations between plasma levels of PCa-related miRNAs and PCa aggressiveness, and 3) determine the associations between genetic polymorphisms in miRNA biogenesis pathway genes and plasma levels of miRNAs known to regulate genes in prostate cancer pathways. To increase the potential for translating our results into disease management strategies, we will include miRNAs with cell-line evidence of transcriptional regulation by miRNA promoter methylation and evidence of gene-expression regulation within prostate carcinogenic pathways. This project is built on a previously funded study of metabolic syndrome, PCa aggressiveness, and outcomes (CDMRP award W81XWH-09-1-0203, PI: Isaac Powell, MD). We are building on that study's infrastructure to enroll an additional 300 patients recently diagnosed PCa, ~60% of whom are AA and ~35% of whom have aggressive disease. Data and blood samples for Aim 1 will come from both the 500 men from the previously funded study and 300 additional men from this current study, and for Aims 2 and 3 will come from ~150 men from whom we have obtained a blood sample prior to their receiving PCa treatment. Because many miRNAs are regulated by promoter methylation, they are potential targets for treatment with demethylating agents to prevent or slow PCa carcinogenesis;[2, 3] target miRNAs may vary by race. Identifying risk profiles of men who may benefit from such treatment, based on race, inherited genotypes and/or plasma miRNA levels, will provide momentum for developing the field of personalized medicine.

2. Keywords

prostate cancer, microRNA, racial disparities, African American, genetic polymorphisms, biochemical recurrence, epidemiology

3. Overall Project Summary

Activities during this second year of the project remained focused on Tasks 1 and 2 of the statement of work, as planned. Task 1 (months 1-30) is to obtain blood and data for 300 new study subjects. Between September 30, 2014 and September 29, 2015 (end of reporting period), 59 men (42 AA, 17 EA) were enrolled in the study (Task 1.a), for a total of 612 men

(towards our goal of 800 men). Of these newly enrolled men, blood was collected on 24 so far (Task 1.b), for a total of 483 blood samples available to date. We expect to be able to obtain blood samples on almost all of the 612 enrolled men. Twenty-nine pre-treatment blood samples were collected (Task 1.c), for a total of 115 towards our goal of 150 pre-treatment samples. We are holding off on extracting miRNA from these samples until we are ready to also quantify the miRNA to avoid batch effects and reduce the number of sample freeze-thaw cycles. Questionnaires were completed by 60 men (Task 1.d), for a total of 589 completed questionnaires. Following national trends, the number of prostate cancer patients eligible for the study is declining in the clinic. Our enrollment rate among eligible men is ~95%.

Our facility recently merged with a large healthcare provider network of hospitals (McLaren), and we are working to open recruitment at one or two of the larger sites nearby with existing research recruiting infrastructure, which will increase our enrollment rate without significant cost increases.

As described in Task 2 of our statement of work, we have been actively following all of the enrolled men in the cohort (from the previously funded study and from the current protocol) who did not have extensive disease at diagnosis for PSA outcomes. Mean follow-up time is currently 57 months. Follow-up of PSA test results through medical records and Caisis database have just been updated, and a linkage with Metropolitan Detroit SEER registry (MDCSS) for vital status will be repeated prior to final analyses.

4. Key research Accomplishments

Nothing to report.

5. Conclusion

We plan to continue to enroll men in the study and collect blood, questionnaire, clinical, and outcomes data through month 30. At month 30, we plan to begin genotyping all available blood samples using the Illumina Mega array (Task 3). This panel has excellent coverage of SNPs within the microRNA biogenesis pathway genes of interest, and our genomics core has experience successfully running this panel in similar samples. The initial proposed genotyping plan to evaluate a custom panel of ~384 SNPs using the Illumina GoldenGate® genotyping platform is no longer commercially available.

At month 30 we will also measure circulating miRNA levels in ~150 men with pre-treatment plasma available (Task 4). Following these assays, we will analyze the data as outlined in Task 5 of the statement of work for publication in months 30-36. Analyses are as follows:

a. Perform logistic regression analyses of associations between SNPs, haplotypes and PCa aggressiveness and prepare related manuscript
b. Perform Cox proportional hazard analyses of associations between SNPs, haplotypes and PCa recurrence and prepare related manuscript
c. Perform logistic regression analyses of associations between plasma levels of miRNAs and aggressiveness and prepare related manuscript.
d. Perform Analysis of Covariance to associate genetic polymorphism with plasma levels of miRNAs, and prepare related manuscript

6. Publications, Abstracts, and Presentations

Nothing to report.

7. Inventions, Patents and Licenses

Nothing to report.

8. Reportable Outcomes

Nothing to report.

9. Other Achievements

Nothing to report.

10. References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64: 9-29.

2. Kong D, Banerjee S, Ahmad A, et al. Epithelial to mesenchymal transition is mechanistically linked with stem cell signatures in prostate cancer cells. PLoS One. 2010;5: e12445.

3. Kong D, Heath E, Chen W, et al. Epigenetic silencing of miR-34a in human prostate cancer cells and tumor tissue specimens can be reversed by BR-DIM treatment. Am J Transl Res. 2012;4: 14-23.

11. Appendices

Nothing to report.